Management of intractable epilepsy

J H Livingston

Intractable epilepsy is a common problem confronting the paediatrician. Although there is little epidemiological data available, it is estimated that 10 to 20% of childhood epilepsies are intractable.¹

Intractability here is taken to mean epilepsy that is not controlled after an adequate (see below) trial of first line conventional anti-epileptic drugs treatment, singly and in combination. It is not the frequency of seizures as such that defines them as intractable, but rather their resistance to control by treatment.

When confronted with a child with apparently intractable epilepsy, three questions need to be considered: (1) Does the patient have epilepsy? (2) What is the underlying cause/diagnosis? (3) Is the epilepsy truly intractable?

(1) Does the patient have epilepsy

It is estimated that 20 to 30% of patients referred for management of intractable epilepsy do not have epilepsy.^{2,3} In the assessment of paroxysmal disorders the most important aspect is the history. This history needs to be from both the patient and one or more eye witnesses.

The largest group of disorders mistaken for epilepsy are the various forms of anoxic seizures or syncopal attacks. This has been comprehensively discussed by Stephenson in his recent monograph.⁴ Migraine is another important group with a complex inter-relationship with epilepsy. There are a large number of less common non-epileptic paroxysmal disorders in childhood⁵ and it behoves the clinician who deals with epilepsy to be familiar with them. There are also undoubtedly some disorders that are incompletely understood that are difficult to classify as epileptic or otherwise. Psychic seizures and pseudoseizures are another important group. It should be remembered that pseudoseizures are more common in patients with epilepsy than in those without.

Complementary information is given by the electroencephalogram (EEG). Paroxysmal activity on the EEG does not mean that a patient's attacks are necessarily epileptic in nature. Recording a seizure during an EEG is extremely helpful. In cases with very frequent attacks, long term monitoring with a video EEG and polygraphy may help resolve the issue.

If there is persistent doubt about the diagnosis then it is better to wait and see before starting treatment. If the patient is already on treatment the antiepileptic drugs can be gradually reduced and the effects observed.

(2) What is the underlying cause/diagnosis?

In some cases the cause is obvious, for example asphyxial brain damage, congenital infection, or cerebral malformation. However, in many cases this is not so and there is always the question of whether there is an underlying neurodegenerative disease.

All cases of intractable epilepsy should have a high resolution computed tomography, and ideally, magnetic resonance imaging performed. With these imaging techniques an increasing number of neuronal migration disorders, focal or generalised, are being detected.⁶ A follow up computed tomogram should also be carried out after three to four years if the cause is in doubt, particularly in cases where there is clearly a focal EEG abnormality or seizure pattern. In this way very slow growing tumours, such as oligodendrogliomas, may be detected.

Although there are a large number of neuro-metabolic diseases in which seizures are prominent, most of these will be suggested by other clinical features. There are, however, a few conditions in which intractable epilepsy may be the most prominent initial feature, and in which the other clinical features may be difficult to detect against the background of intractable epilepsy (table). Pyridoxine dependency should always be excluded, particularly in infantile epilepsy.⁷

As well as a diagnosis of specific disease entities it is also important to try and make a diagnosis of the type of epilepsy or epileptic syndrome,^{8,9} as this helps in giving a prognosis, choice of treatment, and in research.

(3) Is the epilepsy truly intractable?

Epilepsy is often labelled 'intractable' when it is not. There are several causes of such 'pseudo-intractable epilepsy'.¹⁰ When reviewing the history of previous treatments it is necessary to document the following for each antiepileptic drug: the duration of treatment, dose/kg, clinical effects, side effects, and blood concentrations (where appropriate). If a drug has been stopped

Progressive diseases which may present with intractable epilepsy before other clinical features are prominent

Age of onset	Disease
Neonate	Non-ketotic hyperglycinaemia Molybdenum cofactor deficiency Menkes' disease Late infantile neuronal ceroid lipofuscinosis Progressive neuronal degeneration of childhood Huntington's disease
Teenage	Progressive myoclonus epilepsy syndromes ²⁴

Clarendon Wing,
The General Infirmary at
Leeds, Belmont Grove,
Leeds LS2 9NS

Correspondence to:
Dr Livingston.

after a very short time the reason for changing it needs to be determined. When such a drug history is available it should be clear whether there has been an adequate trial of each drug, alone or in combination. Given the spontaneously fluctuating nature of most epilepsies, each trial of drugs or combination should be given for a minimum of one month (unless there is an acute severe deterioration). For this reason it is normally preferable that drug changes occur at home and are monitored in outpatients rather than in hospital. This has the added benefit of preventing doctors succumbing to the seemingly irresistible temptation to change antiepileptic drugs every few days in a hospitalised child with uncontrolled seizures. It is also important to decide whether an adequate dose of each drug has been given. In this respect the concept of a 'therapeutic range' of blood concentrations of antiepileptic drugs is not particularly helpful. This is particularly so for sodium valproate and carbamazepine. (If a patient with intractable epilepsy on sodium valproate or carbamazepine has no apparent side effects, then these can be reasonably increased despite a blood concentration in the so called therapeutic range.) Persistently low blood concentrations may however, indicate non-compliance, which is an important cause of poor seizure control.¹¹

A drug history such as this may reveal that an insufficient trial of one or more drugs may have been given and in some patients going back to an antiepileptic drug that has previously been tried in a different dose or combination is sufficient to control the seizures. The possibility that the treatment is making the epilepsy worse must always be considered. It is probable that all the commonly used antiepileptic drugs can at some time or other aggravate seizures.

In someone with continuous seizures there is no justification for polytherapy. Occasionally seizures will improve on decreasing or stopping drugs,¹² more often however, the seizures remain the same, but alertness and coordination improve.

The benzodiazepines warrant special mention because of their often dramatic effect in improving seizures. They are, however, a very frustrating group of drugs in that tolerance to their effects develop in at least two thirds of cases. In addition side effects are often considerable (cognitive impairment, behavioural disturbance). Clobazam probably results in fewer behavioural side effects than the other benzodiazepines. There are, however, some patients who respond well to benzodiazepines without side effects and do not develop tolerance. Another difficulty with the benzodiazepines is the occurrence of withdrawal seizures on decreasing the dose. This is often done too fast resulting in reluctance on the part of the parents to try again. Benzodiazepines should be decreased very slowly in small steps, no faster than every two to four weeks.

Surgical treatment

Any patients with intractable epilepsy should be considered as a possible candidate for surgical treatment. The indications for surgical treat-

ment are being increasingly refined¹³ as it is clear that outcome is critically dependent on selection criteria. Surgery is most likely to be of benefit for intractable partial epilepsy, the best results being from series of temporal lobectomies carried out for complex partial seizures.¹⁴ Extratemporal resection may be of benefit. In patients with a hemiplegia and intractable epilepsy arising from an abnormal hemisphere, hemispherectomy may be dramatically beneficial.¹⁵ Section of the corpus callosum (partial or complete) has been recommended for patients with intractable drop attacks and other generalised seizures. Adverse affects are few but some patients have become worse. The exact place of this procedure has not yet been determined.¹⁶ Even if the underlying cause of the epilepsy is a generalised disorder such as tuberous sclerosis consideration should be given to surgical treatment if the seizures appear to arise from one particular area.

It is beyond the scope of this article to discuss in detail all aspects of surgical treatment of the epilepsy. It is clear, however, that surgical treatment should be considered earlier than has usually been the case.

Having established that the child has true intractable epilepsy and that surgery is not likely to be of benefit an attempt should be made to reduce antiepileptic drug treatment to the minimum that controls unacceptable seizures. This is necessarily vague as what is acceptable for the child, family, doctor, or school will vary from patient to patient. If a child has occasional prolonged seizures only, that cannot be prevented by continuous treatment it may be more appropriate to discontinue regular treatment and for the parents to keep a supply of rectal diazepam or paraldehyde to use in the event of such a seizure. It is often helpful to determine what is the most troublesome type of attack and maintain the child on the drugs that appeared to help this seizure the most.

Having decreased conventional antiepileptic drug treatment to a minimum, consideration needs to be given to other types of treatment. It is not the purpose of this article to list all the agents that have been tried in intractable epilepsy. One of the reasons why it is unclear whether such treatments work or not is because they are rarely used in a systematic or controlled way with outcomes adequately defined or documented. The lack of adequate studies makes interpreting the reported efficacy of each of the following treatments difficult if not impossible. Although such evaluation is time consuming and complex, it is essential in order to interpret the effects of a new treatment.

Dietary treatment

The ketogenic diet may be successful in controlling seizures, particularly in young children.¹⁷ The various different diets all appear to be effective.

Food allergy as a cause or contributor to epilepsy has been proposed recently. A trial of the so called 'oligoantigenic' or few foods diet showed improvement in seizures in 50% of the children studied. The responders were children

who had symptoms of migraine as well as epilepsy.¹⁸ The placebo effect of such diets is very strong, however, and although enormously complex to design and interpret, further studies are needed.

Steroids

Claims have been made for the efficacy of steroids in Landau-Kleffner syndrome, non-convulsive status epilepticus, and the syndrome of electrical status epilepticus of sleep. Though individual patients undoubtedly may respond, with the possible exception of some cases of Landau-Kleffner syndrome, there is currently no clear indication for long term steroid treatment in intractable epilepsy.

Immunoglobulins

Immunoglobulins have been used in the treatment of intractable epilepsy for a number of years. Most, but not all, studies have reported benefit.¹⁹ Several studies have suggested that those with selective IgG₂ deficiency are more likely to respond and some long term responses have been described.²⁰ The optimal dose has not yet been determined. Although expensive, immunoglobulins are safe and warrant further study.

New antiepileptic drugs

There are at the moment at least 10 new antiepileptic drugs undergoing clinical evaluation and others at the preclinical evaluation stage. Vigabatrin has recently become available for general use and appears particularly useful against partial seizures. It may also be effective in the treatment of infantile spasms, but it appears less successful against other types of intractable epilepsy in childhood.^{21 22}

Lamotrigine is likely to become available in the next few years for general use. Its role is not yet clear, but it has been of benefit in some studies (SJ Wallace, abstract presented at British Paediatric Neurology Association (BPNA) 1989, J Gibbs *et al.*, abstract presented at BPNA 1991).

Non-pharmacological treatment

In all cases of epilepsy, whether intractable or not, an exhaustive search should be made for precipitating or aggravating factors. This may reveal that the epilepsy is a reflex epilepsy and can be treated by avoiding the precipitating stimulus, with or without antiepileptic drugs.²³ In intractable epilepsy that is not reflex there may none the less be factors internal or external that precipitate or aggravate seizures. This has led to attempted behavioural treatments of epilepsy, either by biofeedback methods or using relaxation techniques.¹¹ This is most likely to be of value when there is an obvious warning before the seizure occurring, or when tension and anxiety seems to aggravate seizure frequency. Research is needed to evaluate these techniques in younger children and those with more severe cognitive impairment.

The social, emotional, and educational effects of intractable epilepsy on the child and the functioning of the family are often devastating. Because of the fluctuating nature of epilepsy, it is very difficult for any sort of normal adjust-

ment process to loss or disease to occur. When the epilepsy is clearly intractable it is important that the parents are told this and helped to understand it. The goals of treatment need to be redefined. At the same time this must be balanced with keeping some hope alive. This is both necessary and justifiable. Schooling is often extremely difficult and children may be unable to be accommodated even in special schools. This is one situation where there is a real place for residential schools for children with epilepsy. Once in such an environment the stigma of having epilepsy will often evaporate and the child may improve significantly.

Future research should be directed towards the development of new drugs, the development of surgical treatments, towards developing better ways of analysing the response to anti-epileptic drugs, and for quantifying seizure frequency more accurately.

It is to be hoped that in the 'decade of the brain' new insights into the basic mechanism of intractable epilepsy will be gained that will ultimately lead to better treatments.

- 1 Brorson LO, Wranne L. Long term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987;28:324-30.
- 2 Jeavons PM. Non-epileptic attacks in childhood. In: Rose FC, ed. *Research progress in epilepsy*. London: Pitman, 1983:224-30.
- 3 Robinson R. When to start and stop anticonvulsants. In: Meadow R, ed. *Recent advances in paediatrics*. Vol 7. Edinburgh: Churchill Livingstone, 1984:155-74.
- 4 Stephenson JBP. *Fits and saints. Clinics in developmental medicine*. No 109. Oxford: Mackeith Press, 1990.
- 5 Aicardi J. Diagnosis and differential diagnosis. *Epilepsy in children*. New York: Raven Press, 1986:287-308.
- 6 Anonymous. Epilepsy and disorders of neuronal migration. [Editorial.] *Lancet* 1990;336:1035.
- 7 Goutieres F, Aicardi J. Atypical presentations of pyridoxine dependent seizures: a treatable cause of intractable epilepsy in infants. *Ann Neurol* 1985;17:117-20.
- 8 Roger J, Dravet C, Bureau M, *et al.*, eds. *Epileptic syndromes in infancy, childhood and adolescence*. London: John Libbey, 1985.
- 9 Aicardi J. *Epilepsy in children*. New York: Raven Press, 1986.
- 10 Aicardi J. Clinical approach to the management of intractable epilepsy. *Dev Med Child Neurol* 1988;30:429-40.
- 11 Schotte DE, DuBois MA. Behavioural medicine approaches to enhancing seizure control in children with epilepsy. In: Hermann BP, Seidenberg M, eds. *Childhood epilepsies: neuropsychological, psychosocial and intervention aspects*. Chichester: John Wiley, 1989:189-200.
- 12 Schmidt D. Reduction of two-drug therapy in intractable epilepsy. *Epilepsia* 1983;24:368-76.
- 13 Wylie E. Cortical resection for children with epilepsy. *Am J Dis Child* 1991;145:314-20.
- 14 Wylie E, Luders H, Hetal MH. Clinical outcome after complete or partial cortical resection for intractable epilepsy. *Neurology* 1987;37:1634-41.
- 15 Rasmussen T, Villemure JG. Cerebral hemispherectomy for seizures with hemiplegia. *Cleve Clin J Med* 1989;56(suppl):S62-8.
- 16 Wylie E. Corpus callosotomy for intractable generalised epilepsy. *J Pediatr* 1988;113:255-61.
- 17 Schwartz RH, Eaton J, Aynsley-Green A, Bower BD. Ketogenic diets in the management of childhood epilepsy. In: Rose FC, ed. *Research progress in epilepsy*. London: Pitman, 1983:326-32.
- 18 Egger J, Soothill JF, Carter CM, Wilson J. Oligoantigenic diet in epilepsy. *Lancet* 1983;ii:865-9.
- 19 Illum N, Taudorf K, Hielmann C, *et al.* Intravenous immunoglobulin: a single-blind trial in children with Lennox Gastaut syndrome. *Neuropediatrics* 1990;21:87-90.
- 20 Plebani A, Duse M, Tiberti S, *et al.* Intravenous-gamma-globulin therapy and serum IgG subclass levels in intractable childhood epilepsy. *Monogr Allergy* 1988;23:204-15.
- 21 Luna D, Dulac O, Pajot N, *et al.* Vigabatrin in the treatment of childhood epilepsies: a single-blind placebo-controlled study. *Epilepsia* 1989;30:430-7.
- 22 Chiron C, Dulac O, Beaumont D, *et al.* Therapeutic trial of vigabatrin in refractory infantile spasms. *J Child Neurol* 1991 (in press).
- 23 Wilkins A, Lindsay J. Common forms of reflex epilepsy: physiological mechanisms and techniques for treatment. In: Pedley TA, Meldrum BS, eds. *Recent advances in epilepsy*. Vol 2. Edinburgh: Churchill Livingstone, 1985:239-72.
- 24 Berkovic SF, Andermann F. The progressive myoclonus epilepsies. In: Pedley TA, Meldrum BD, eds. *Recent advances in epilepsy*. Vol 3. Edinburgh: Churchill Livingstone, 1986:157-88.